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ELLEN P. WINNER  
GREENLEE & ASSOCIATES  
5370 MANHATTAN CIRCLE, STE. 201  
BOULDER, CO 80303

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on May 31, 1990 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), \_\_\_\_\_ days from the date of this letter.  
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- ☒ Notice of References Cited by Examiner, PTO-892. 4pp
- ☒ Notice re Patent Drawing, PTO-948.
- ☒ Notice of Art Cited by Applicant, PTO-1449. 1p
- ☐ Notice of Informal Patent Application, Form PTO-152
- ☐ Information on How to Effect Drawing Changes, PTO-1474.
- ☐

Part II SUMMARY OF ACTION

- ☒ Claims 15-25 are pending in the application.  
Of the above, claims \_\_\_\_\_ are withdrawn from consideration.
- ☒ Claims 1-14 have been cancelled.
- ☐ Claims \_\_\_\_\_ are allowed.
- ☒ Claims 15-25 are rejected.
- ☐ Claims \_\_\_\_\_ are objected to.
- ☐ Claims \_\_\_\_\_ are subject to restriction or election requirement.
- ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
- ☐ Formal drawings are required in response to this Office action.
- ☐ The corrected or substitute drawings have been received on \_\_\_\_\_. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
- ☐ The proposed additional or substitute sheet(s) of drawings, filed on \_\_\_\_\_, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
- ☐ The proposed drawing correction, filed \_\_\_\_\_, has been ☐ approved; ☐ disapproved (see explanation).
- ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. \_\_\_\_\_; filed on \_\_\_\_\_.
- ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
- ☐ Other

Claims 1-14 have been cancelled. Claims 15-25 remain.

The application should be reviewed for errors. For example, page 132, line 15, "35X"; page 152, line 15 "form."

Claims 15-25 are rejected under 35 U.S.C. 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite "a Bacillus thuringiensis crystal protein" (Claim 15(a), for example). However, Applicants have enabled the claimed invention for only one B. thuringiensis crystal protein which sequence is shown in Figure 1. Not only do different varieties of B. thuringiensis have different insecticidal proteins with varying homology to each other, but the same variety of B. thuringiensis may have several insecticidal proteins. For example, Thorne et al points out that the subspecies kurstaki crystal contains at least 3 proteins with insecticidal activity (page 801, column 2, top, marked section; see other marked sections as well on pages 801 and 808-809). See also, Hofte et al, especially Tables 1-5. Therefore, it is necessary for Applicants to specify the particular B. thuringiensis var. kurstaki crystal protein claimed.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention. Much of the data, especially on the effects of the transformed tissue on insect

mortality, includes no control for comparison purposes and to determine the baseline viability of the insects, for example present specification, page 122, trials 1 and 2; and Tables 8 and 9 which tests toxicity of tobacco leaves transformed with full length B.t.; also page 123, trial 3 and page 124, trial 5.

- 5 Comparison to control plants would be essential, given problems with the bioassay such as "wondering worms" discussed by Applicants themselves (see present specification, page 152, for example).

10 In trial 4, although a non-transformed, regenerated plant is used as a control, a plant transformed with the same plasmid lacking the insecticidal sequence was not tested. In this trial, 2 of the 5 clones give % mortality of less than the control and one clone is about the same as the control. Of the two clones which gave significantly high results, one was from a chimeric plant from which the insecticidal activity was lost. Thus, only clone 100 produced insecticidal tissue and the viability of this plant is not clear as it

15 apparently had fewer leaves than the other clones (page 123, line 5) and many R<sub>0</sub> plants were infertile (present specification, page 153, for example) or marginally fertile (present specification, page 156, first full paragraph). Furthermore, there is reason to doubt that the gene would be transferred to and expressed in progeny (see Vaeck et al, page 36, column 1, "Inheritance of the protection"). Of the 5 trials, this one is the most persuasive that

20 Applicants' data has any meaning and, even in this case, there is no control plant transformed with the same plasmid lacking the insecticidal sequence, and the data indicates a high level of unpredictability and variability. Because there is no control plant transformed with the same plasmid lacking

25 the insecticidal sequence which was a routine control as shown by similar work in the art such as Vaeck et al, trial 4 is also objected to.

In Trial 3, page 123, there is no indication as to which way the scale goes, i.e., does rank 1 correspond to large or small leaves? Consequently, the specification does not sufficiently describe the insecticidal properties of the

30 transformed tobacco plant cells expressing a full-length B.t. gene.

In Table 11, 5 callus samples indicated expression of insecticidal protein in both tests. However, presence of the insecticidal protein is not a reliable indicator that the cell is insecticidal because levels may be too low to provide sufficient quantities of the protein to be toxic to insects. See Vaeck et al, pages 35-36, bridging paragraph, for example. This objection also applies to other data presented such as that for potato (Example 16) and cotton (Example 17). Furthermore, it is not clear what is the source of the B.t. containing plasmid in the protocol shown on page 141, present specification. Thus, Examples 14, 16, and 17 and Table 11 are not enabling for claims to other insecticidal plant cells.

Table 14 (Example 15), like Trial 4, above, is defective in that there is no demonstration of the insecticidal activity of a plant transformed with the same plasmid lacking the insecticidal sequence. The use of such a control is routine in the art as shown by Vaeck et al, for example.

Claims 15-25 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification.

Claim 15-16, 19, and 22-25 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to dicot cells. See MPEP 706.03(n) and 706.03(z). There is no evidence in the specification that the claimed invention is enabled for plant species in general. Plant species vary with respect to their ability to undergo transformation and regeneration. Applicants have exemplified only one non-dicot species in the present specification, that is, maize, Example 14. However, insecticidal activity of the transformed tissue was not demonstrated and expression of the protein was demonstrated only in calli. As taught by Jordan et al transformed callus does not necessarily regenerate transformed shoots. Since the transformed tissue is sicker than the non-transformed tissue, it grows faster. The tissue appears transformed as long as there is some transformed tissue remaining. However, the healthier, non-transformed

tissue no longer tests positive once it has outgrown the transformed tissue and the transformed tissue has died out. It is noted and Applicants point out that the results showed a high degree of variability and non-reproducibility. This would further indicate that the transformation of the calli was not  
5 stable and that any tissue regenerated would be formed from healthier, non-transformed calli contaminating the transformed tissue. Additionally, Barton et al teach that plant cells transformed with Bt were sick. Thus it is doubtful that one skilled in the art would be able to regenerate transformed monocot plants based upon the disclosure of Applicants.

10 It is also noted that regeneration of monocot plants was not a routine procedure at the time of Applicants' claimed priority date or even at the time of filing 07/260,574. It was not within the ordinary level of skill in the art to regenerate monocot plants from the callus exemplified in Example 14. See Vasil, especially pages 400-401, for a discussion of the state of the art  
15 with respect to monocot transformation and regeneration in 1988. Consequently, enablement for Applicants' claimed invention is limited to dicot species.

Claims 15-25 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited <sup>to</sup> a full length Bacillus  
20 thuringiensis crystal protein gene where the insecticide encoding fragment is the insecticide encoding fragment found in any of pH450, pH577, or pH578 and the plant or plant cell is either of tomato or tobacco, and the toxic activity is directed against Manduca sexta. See MPEP 706.03(n) and  
25 706.03(z). Expression of a bacterial gene, especially B. thuringiensis toxins, in a plant cell is highly unpredictable as shown by Vaeck et al, Fischhoff et al and Barton et al, for example. Furthermore, a given B. t. toxin does not show toxicity against all insect species (See Hofte et al, Table 5; Vaeck et al, page 37, column 1, for example). Applicants have provided reasonable guidelines to enable one skilled in the art to obtain the claimed invention without

undue experimentation only for the plant and insect species, and DNA sequences recited above.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this  
5 Office action:

"A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent."

10 (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States."

Claims 16 and 23 are rejected under 35 U.S.C. § 102 (b) as being anticipated by either of Vaeck et al or Fischhoff et al. Vaeck et al and  
15 Fischhoff et al disclose plant and plants cells which were insecticidal due to expression of truncated forms of a B.t. toxin gene. Although Vaeck et al actually uses B.t. sequences from a different strain than that used by Applicants, Applicants' claims are so broadly recited that they are anticipated by either of Vaeck et al or Fischhoff et al. It is noted that  
20 Applicants are not entitled to the filing date of the parent application with respect to claims to truncated versions of the B.t. gene. It is also noted that Applicants have not enabled claims directed towards use of a truncated version of a B.t. toxin gene in the present application.

Claims 15, 16, 18, and 22-25 are rejected under 35 U.S.C. § 102 (a)  
25 (with respect to parent application 06/848,733) as being anticipated by De Greve et al (EP-A 193259). De Greve et al disclose plant and plants cells which were insecticidal due to expression of both full length and truncated forms of a B.t. toxin gene. Although the truncated forms worked better than the full length forms, the full length form of the gene also had an insecticidal  
30 effect (see, for example, Example 13.2). It is noted that the De Greve et al

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reference predates the parent application 06/848,733. Insecticidal, transformed plants and plant cells and truncated genes are not enabled in the grandparent application 06/535,354.

5 The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

10 "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15 Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person."

20 This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to  
25 consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

30 Claims 16 and 23 are rejected under 35 U.S.C. 103 as being unpatentable over either of Vaeck et al or Fischhoff et al taken with Wong et al, Held et al, or Klier et al. Vaeck et al and Fischhoff et al disclose plant and plants cells which were insecticidal due to expression of truncated forms of a B.t. toxin gene. Although Vaeck et al actually uses B.t. sequences from a different strain than that used by Applicants, Applicants' claims are so

5 broadly recited that they are obvious over either of Vaeck et al or Fischhoff et al. Furthermore, use of sequences from the same strain as disclosed by Applicants or other B.t. strains in place of the insecticidal genes employed by Vaeck et al or Fischhoff et al would be obvious in view of the availability of such sequences as taught by Wong et al or Held et al or Klier et al. It is noted that Applicants are not entitled to the filing date of the parent application with respect to claims to truncated versions of the B.t. gene. Therefore, the Vaeck et al and Fischhoff et al references may properly be applied to claims to a truncated B.t. gene expressed in plants.

10 Consequently, the modification of the methods for producing insecticidal plants and plant cells taught by Vaeck et al and Fischhoff et al using other B.t. toxin genes was well within the ordinary skill in the art at the time the claimed invention was made as adequately demonstrated by the secondary references. One of ordinary skill would have had a reasonable  
15 expectation of success in view of the availability of B.t. sequences as indicated by the references and the guidelines provided by either Fischhoff et al or Vaeck et al. Thus the claimed invention as a whole was clearly prima facie obvious over the references, in the absence of sufficient, clear, and convincing evidence to the contrary.

20 Claims 15-25 are rejected under 35 U.S.C. 103 as being unpatentable over De Greve et al (EP-A 193259) taken with Wong et al, Held et al, or Klier et al. De Greve et al disclose plant and plants cells which were insecticidal due to expression of both full length and truncated forms of a B.t. toxin gene. Although the truncated forms worked better than the full length forms, the  
25 full length form of the gene also had an insecticidal effect (see, for example, Example 13.2). It is noted that the De Greve et al reference predates the parent application 06/848,733. Insecticidal, transformed plants and plant cells and truncated genes are not enabled in the grandparent application 06/535,354. Therefore, application of the De Greve et al reference to the  
30 present claims is proper.

While De Greve et al may not use exactly the same insecticidal gene sequences as claimed by Applicants, use of sequences from the same strain as disclosed by Applicants or other B.t. strains in place of the insecticidal genes employed by De Greve et al would be obvious in view of the  
5 availability of such sequences as taught by Wong et al or Held et al or Klier et al.

Consequently, the modification of the methods for producing insecticidal plants and plant cells taught by De Greve et al using other B.t. toxin genes was well within the ordinary skill in the art at the time the  
10 claimed invention was made as adequately demonstrated by the secondary references. One of ordinary skill would have had a reasonable expectation of success in view of the availability of B.t. sequences as indicated by the references and the guidelines provided by De Greve et al. Thus the claimed invention as a whole was clearly prima facie obvious over the references, in  
15 the absence of sufficient, clear, and convincing evidence to the contrary.

Claims 15-21 and 23-25 are rejected under 35 U.S.C. 103 as being unpatentable over Bevan et al, Fraley et al, Herrera-Estrella et al, or Barton et al. taken with Wong et al, Held et al, or Klier et al et al further in view of Brinster et al. The primary references teach cloning and expressing foreign  
20 genes in plant cells by using a DNA vector having a plant expressible promoter (e.g. the T-DNA nopaline synthetase promoter) controllably linked to a foreign gene. Additionally, Bevan et al and Herrera-Estrella et al indicate that it is now conventional to regenerate plants from single cells. The secondary references teach the cloning and expression of insecticidal  
25 structural genes. Brinster et al teach fusing a foreign structural gene to the promoter sequence of an eukaryotic DNA in a eukaryotic cell so as to enable expression of the foreign gene in the resulting eukaryotic organism.

Consequently, the modification of the methods taught by the primary references with known sequences was well within the ordinary skill in the

art at the time the claimed invention was made as adequately demonstrated by the secondary and tertiary references. One of ordinary skill would have had a reasonable expectation of success in expressing insecticidal Bt toxin genes in plant cells in view of the cited references. Thus the claimed  
5 invention as a whole was clearly prima facie obvious over the references, in the absence of sufficient, clear, and convincing evidence to the contrary.

The Remarks and the Declaration of Dr. Adang filed April 17, 1989 have been considered in formulation of the rejections and objections set forth above.

10 No claim is allowed.

An inquiry concerning this communication should be directed to Che S. Chereskin, Ph.D., at telephone number (703) 308-0034. Inquiries of a general nature should be directed to the Group 180 secretary at (703) 308-0196.

15 CSE  
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*Elizabeth C. Weimar*  
ELIZABETH C. WEIMAR  
SUPERVISORY PATENT EXAMINER  
GROUP ART UNIT 184